REMARKS

Claims 1-13 and 16-34 are pending in this application. Claims 1-12 and 20-30 have been withdrawn from consideration as being drawn to a non-elected invention. Claims 14 and 15 have been canceled. Claims 13, 16, 17-19, and 31-34 are currently under examination. Claims 17 and 19 have been allowed. Claims 13, 16, 18, and 31-34 have been rejected. Claims 31 and 34 have been amended. Support for the amendments can be found in the currently pending claims and throughout the specification as indicated below.

Applicants gratefully acknowledge the withdrawal of the prior objection to claims 17 and 19 for being dependent upon rejected claims. It is recognized and acknowledged that claims 17 and 19 are currently allowed.

Applicants also acknowledge the withdrawal of the prior rejection of claims 13, 16, and 18 under 35 USC 112, first paragraph, and 35 USC, second paragraph.

Applicants also acknowledge the withdrawal of the prior rejection of claims 13 and 16 under 35 USC 102(a).

In light of the following remarks, Applicants respectfully request reconsideration of this application and allowance of the pending claims to issue.

35 U.S.C. § 112, second paragraph

Claims 31-34 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter the Applicants regard as the invention. Specifically, the claims which recite "A nucleic acid encoding a mosaic protein comprising more than two homologous antigenic peptides from different genotypes or subtypes of a species" have been rejected for failing to "indicate what these genotypes or subtypes are a species of." Applicants have amended claims 31 and 34 to recite "of Hepatitis C virus." Support for this amendment can be found throughout the original claims and specification. These amendments were made solely to expedite prosecution and are

in no way limiting as the claims were clear as previously written. Applicants believe that this rejection has been overcome and respectfully request its withdrawal.

35 U.S.C. § 103

A. The rejection of claims 13, 16 and 18 under 35 U.S.C. § 103 (a) as allegedly being unpatentable over Khudyakov et al., in view of Zhang et al., Bukh et al. and Chien et al. was maintained. In particular, the Examiner states that the amendment to claim 13, does not avoid the prior art as asserted by the applicants and that a prima facie case of obviousness has been met. In order for cited art to rise to the level of rendering a claim obvious, "[f]irst there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one or ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art must teach or suggest all the claim limitations." (MPEP 2143)

With respect to the amendment to claim 13, applicants amended the claim to recite "homologous regions of the same protein." The Examiner did not find this amendment persuasive as the Examiner contends that "Zhang teaches the use of multiple epitopes from homologous regions of the same protein," and therefore, "it would have been obvious to those in the art to have used them in the fusion protein suggested by Khudyakov and Chien." Applicants respectfully traverse the rejection. Contrary to the Examiner's assertion that Zhang teaches the use of multiple epitopes, Zhang does not actually use the epitopes in combination but as a panel of epitopes to be used to distinguish antibodies. A thorough reading of Zhang reveals that no mixture of peptides was used in the Enzyme Immunoassays and though the Inhibition assays do employ peptide mixtures, these mixtures are used to identify antibodies not specific to any of the peptides of the panel (ie. of an unknown genotype providing for only cross-reactive protection which would result in incomplete inhibition). As the sequence differences were known prior to Zhang, this rejection has no more weight than a rejection based on a sequence comparison of the genotypes and stating it would be obvious to use the different epitopes. Since the Examiner is

relying on Zhang et al. for the teaching the use of "more than two homologous antigenic peptides from the same domain from different genotypes," the combination of Zhang, Khudykov, and Chien do not teach or suggest all of the claim limitations.

Furthermore, there is no teaching or suggestion in the art that would provide motivation for the combination of Khudyakov, Chien, and Zhang. Such a combination of art is only obvious, and thus a rejection is only possible, when one is aware of the art disclosed in the present application, and therefore such a rejection utilizes impermissible hindsight. Moreover, Khudyakov specifically teaches away from the combination of proteins in methods such as those taught by Zhang et al. in the paragraph spanning pages 7072-7073. In this paragraph, Khudyakov states that "[a]bsorption of several different proteins in one microtiter well often may result in an overall decrease of sensitivity to each protein." Thus, Khudyakov would teach away from its combination with the method of Zhang et al.

With regard to the combination of Khudyakov and Chien, the Examiner asserts that the cited art do provide motivation to combine the references. In particular the Examiner continues to assert that Khudyakov makes "constant indications in the reference that the article is concerned with strategies for constructing such proteins, rather than a disclosure limited to HEV, provides adequate motivation to look to the combination of this reference with others teaching like proteins." The Examiner then states as support for the inclusion of HCV among the "other pathogens" the paragraph spanning pages 7072-7073 which mentions HCV. However, the mention of a virus does not mean the intention would be to use the mosaic protein detailed in the reference with that virus. In fact the reference to HCV is made in the context of a technique used in overcoming an "overall decrease of sensitivity to each protein," in an assay detecting "several different proteins in one microtiter well."

Although Chien et al. do overcome the problems encountered by Zhang, the mosaic protein disclosed by Chien et al. is markedly different from either that disclosed by Khudyakov or that disclosed in the present application. More specifically, Chien et al disclose a mosaic protein composed of heterologous epitopes from different protein domains. Khudyakov

discloses a mosaic protein with only one homologous antigenic peptide from the same domain. By contrast the present claims specify "more than two homologous antigenic peptides from the same domain from different genotypes." Indeed, simply because Khudyakov et al. detail the work done by Chien et al., and Chien et al. happened to use HCV for their mosaic protein, does not mean that Khudyakov was contemplating that HCV could be used in their disclosed method. Had Chien et al. used a different virus for their work, that virus would be listed in place of HCV. Additionally, as the mosaic proteins discussed in Chien et al. and Khudyakov et al. are so different there is no indication that HCV would work in the method of Khudyakov et al. In fact, Khudyakov states quite clearly on page 7073, first column, second paragraph, that "combining many different protein regions in only one polypeptide chain may not always result in a properly folded mosaic antigen." Khudyakov et al. then states in the same paragraph in column two that "proper modeling of antigenic epitopes within mosaic proteins may require attention to the secondary and tertiary structure and may require the construction of several variants of artificial antigens." Thus Khudyakov et al. is teaching that apart from HEV it is not clear if successful mosaic proteins could be made and that undue experimentation may be required to arrive at such proteins. As has been previously discussed, HCV and HEV are dramatically different viruses. Applicants reiterate that the cited art refers to a number of rather different viruses all termed "hepatitis viruses" and that the similarity in their names masks significant difference in their biology. There is no indication in the cited art that a successful mosaic protein of the variety taught by Khudyakov et al.could be made with HCV without possible major modifications. Thus at best, Khodyakov et al. would be a non-enabling invitation to try HCV. Therefore, there is no cited art that provides any expectation of success.

As neither Khudyakov et al. or Chien et al. disclose the mosaic protein claimed herein, at best, the combination of Khudyakov et al. and Chien et al. is improper "obvious to try." The fact pattern available in this rejection mirrors quite closely that detailed in the MPEP (MPEP 2145 X. B). Specifically, the MPEP states that "[i]n some cases, what would have been 'obvious to try' would have been to vary all parameters or try each of numerous possible choices until one

possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.... In others, what was 'obvious to try' was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." *In re O'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988). Here we have Chien et al. and Khudyakov et al. which both teach mosaic proteins. However, the mosaic proteins disclosed are not only dramatically different from each other, but are different than the mosaic protein disclosed in the present invention. Failure of a mosaic protein to properly present each antigenic determinant included could not be remedied but by repeating the process of constructing a completely new mosaic. Essentially, the prior art requires undue experimentation for all but the simplest mosaics (i.e., those with very few different homologous epitopes) as a result of the techniques used to generate or manipulate those mosaics. It is only through the modification of the disclosed proteins in a manner that is admitted by Khudyakov et al. to be unpredictable at the time the cited art was developed that an HCV mosaic protein could be made. Thus what is obvious is to develop a new technology.

The REAL technique taught by the present application solves certain problems relating to production of effective mosaic proteins having a significant number of different homologous epitopes as would be recognized by those of skill in the art. Applicants would direct the Examiner's attention to page 3, line 27 to page 4, line 11, wherein some of the shortcomings of prior art techniques overcome by REAL are taught. In particular, on page 4, lines 3 to 6, the specification teaches that "the use of PCR is disadvantageous in cases where repeated sequences as designed in the gene," as such sequences are recognized by those of skill in the art of not being effectively amplified or replicated with adequate fidelity, or by ETR which "cannot be used to conveniently express short fragments of the synthetic gene." Each of these shortcomings of the prior art are remedied by use of REAL, the technique clearly taught by the specification. Overcoming these shortcomings in the art is instrumental in providing a reasonable expectation

of success.

In view of this, Applicants submit that the prior art did not provide a reasonable expectation of success of mosaic proteins with the characteristics as claimed and that the present specification does provide a reasonable expectation of success. Accordingly, Applicants submit that claims 13, 16 and 18 are unobvious and are fully-enabled.

B. Claims 13, 16 and 18 are also rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Valenzuela et al., U.S. Patent Number 6,428,792. Specifically, the '792 patent allegedly describes a multiple copy fusion antigen and expression vectors encoding the protein wherein the protein includes at least two copies of a given epitope and wherein a copy is defined to include equivalent antigenic determinant from different strains of the same virus. However, as is discussed by the Examiner in the December 03, 2002 Office Action, "the protein taught by the reference is required to contain at least two non-homologous/non-adjacent epitopes (col. 7, lines 50-55)." This is confirmed again by the Examiner in the August 13, 2003 Office Action when the Examiner states "the reference teaches a protein comprising multiple heterologous epitopes." Thus, Claim 13 does not, as is implicitly acknowledged by the Examiner, correspond to what is actually taught by the '792 patent. As this limitation is a requirement of the '792 patent to function correctly, the '792 patent teaches that the method taught and claimed in the present application, would not be expected to work. Thus the '792 patent teaches away from the present application and in particular claim 13 as this limitation is not required.

Pursuant to the above amendments and remarks, consideration and allowance of the pending application is believed warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

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Respectfully submitted,

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I hereby certify that this correspondence, including any items indicated as attached or included, is being transmitted via facsimile transmission to: Examiner Zachariah Lucas, Mail Stop AF, Art Unit 1648, (703) 872-9306, on the date indicated below.

Gwendolyn D. Spratt

12-15-03
Date